

REMARKS

Claims 1-64 and 71-77 are pending. Claims 1-11 and 13-64 were previously withdrawn from consideration, and claims 65-70 were previously canceled. Claims 73 and 77 have been amended. Claim 78 has been added. No new matter has been added by these amendments.

Applicant thanks the Examiner for consideration of the prior response despite the incorrect claim identifiers.

Withdrawal of Objection to the Claims

Applicant thanks the Examiner for withdrawal of the objections to claims 72 and 76.

Withdrawal of Rejections under 35 U.S.C. §112, Second Paragraph

Applicant thanks the Examiner for withdrawal of the rejection of claims 73 and 75 under 35 U.S.C. §112, second paragraph.

Withdrawal of Rejections under 35 U.S.C. §112, First Paragraph

Applicant thanks the Examiner for withdrawal of the rejection of claims 12, 71, 72, 74-76 under 35 U.S.C. §112, first paragraph for containing new matter.

Applicant thanks the Examiner for withdrawal of the rejection of claims 73-76 under 35 U.S.C. §112, first paragraph and acknowledging that there is no need for a biological deposit.

Withdrawal of Rejections of Claim 12 Under 35 U.S.C. §103

Applicants thank the Examiner for the withdrawal of the rejection of claims for obviousness set forth in the Final Office Action. Applicant submits that the claims as amended remain non-obvious in view of the cited art.

Rejections under 35 U.S.C. §112, Second Paragraph

The Office Action has rejected claim 77 under 35 U.S.C. §112, ¶2 as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Office Action asserts that claim 77 is incomplete for missing a step.

Without agreeing with the rejection, Applicant has amended claim 77 to include the phrase “are cultured” reciting a positive step. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §112, First Paragraph

Enablement

The Office Action has rejected claims 73- 76 under 35 U.S.C. §112, ¶1. The Office Action asserts that the claims while being enabled for an androgen drug screening method culturing a test compound in the presence of the cancer cells claimed for 6 weeks, 13 weeks, or 6 to 13 weeks, it does not support culturing cells for an indefinite amount of time. Applicant respectfully disagrees.

At least two biologically defined endpoints are inherent in the methods.

1. The cell develops resistance to the test compound.

Upon development of resistance to the test compound, the experiment is ended. Additional time in culture will not provide further information. Upon identification of resistant cells in less than six weeks, the compound fails to meet the desired characteristics of the screen. This endpoint is clearly contemplated in the methods.

2. All of the cells in the culture die.

Cells that do not develop resistance have a substantially decreased proliferation rate. For example, on page 78, lines 20 to 22, the specification states:

As a result, the proliferation of LNCaP-cxD11 and LNCaP-cxD2 was significantly promoted by bicalutamide [FIG. 1]. On the other hand, in the

parent line LNCaP-FGC, proliferation was significantly suppressed by bicalutamide [FIG. 1].

Applicant submits that it is well known that cells in culture will eventually die if they do not proliferate, which occurs in cell lines that do not develop resistance, providing an endpoint to the screening method. One of skill in the art would understand that dead cells would not provide any additional information.

Moreover, selection of arbitrary endpoints for experiments is well known in the art. No explicit endpoint is required.

The Office Action notes that one of skill in the art is “a drug discovery technologist with a background in screening anti-hormone response drug therapy for cancer,” i.e., the skill level is high. Applicant submits that such a highly skilled individual would be capable of understanding the endpoints that innately exist in the methods of the invention.

Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §103

The Office Action has rejected claims 12, 71, 72 and 77 under 35 U.S.C. 103(a) as allegedly being unpatentable over Long et al (Can. Res. 60:6630-6640 (2000); cited in the PTO 892 form of 5/15/07) in view of Culig et al. ((Br. J. Can. 81:242-251 (1999); cited in the PTO 892 form of 1/12/07) and Haapala et al., Lab. Invest., 81: 1647-1651, 2001); cited in the IDS of 12/2/04).

The Office Action appears to reject claims 12, 71, 72 and 77 for allegedly being obvious in view of Foury et al (J. Steroid Biochem. Molec. Biol. 66:235-240 (1998); cited in the PTO 892 form of 5/15/07) in view of Culig et al. (Br. J. Can. 81:242-251 (1999); cited in the PTO 892 form of 1/12/07) and Haapala et al., (Lab. Invest., 81: 1647-1651, 2001); cited in the IDS of 12/2/04).

The Office Action has rejected claims 12, 71, 72 and 77 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Taplin et al. (Cancer Research, (1999), pp. 2511-2515, Vol. 59, No. 11; cited in the IDS of 12/2/04) in view of Joly-Pharaboz et al (J. Steroid Biochem. Molec. Biol. 55:67-76 (1995); cited in the PTO 892 form of 5/15/07) and further in

view of Culig et al. ((Br. J. Can. 81:242-251 (1999); cited in the PTO 892 form of 1/12/07) and Haapala et al., Lab. Invest., 81: 1647-1651, 2001); cited in the IDS of 12/2/04).

For the sake of brevity, the rejections will be addressed simultaneously.

The Office Action has characterized claims 12, 71, 72 and 77 as being drawn to a method of screening for anti-androgen drugs which produce little or no cancer resistance, where the method involves culturing an androgen-sensitive cancer cell in the presence of the drug for at least six weeks and determining whether or not the cancer cells proliferate in the presence of the drug (Claim 12), where the cancer cells are human (Claim 71) and the human cancer cells are prostate cancer cells (Claim 72) and where the culture period is at least 13 weeks (Claim 77).

None of the references, either alone or in the combinations provided in the Office Action can make obvious the instantly claimed invention as the references fail to teach or suggest the instantly claimed invention.

The Office Action asserts that Long discloses screening antiandrogen compounds for their in vitro growth inhibitory effects on the androgen-dependent prostate cancer cell line, LNCaP in culture for 9 days, but does not teach culturing for 6 or 13 weeks. The Office Action asserts that Culig teaches anti-androgen withdrawal phenomenon may be in part attributed to mutant ARs detected in prostatic carcinomas, and that bicalutamide -resistant cancer growth starts to appear in vivo in xenografted prostate cancer cells in mice at around 40 days and experiments extending to 65 days. Haapala is relied upon to provide even longer culture times of at least 11 months. The Office Action further asserts that one of skill in the art would be motivated to combine the references to provide the instantly claimed invention.

The Office Action alleges that Foury discloses comparing androgen responsive cell lines (LNCaP, R2 and MOP) in vitro for ability to proliferate in studies comparing two different antiandrogen drugs (CYA and RU 56187), and the Foury observes differences in the cell lines over time, but not for the periods of time set forth in the above claims. These deficiencies are said to be overcome by the alleged teachings of Culig and Haapala as set for the above.

The Office Action alleges that Taplin discloses that AR mutations in tumor cells occur in response to strong selective pressure from flutamide (antiandrogen) treatment in vivo

and that these mutations result in drug resistance for some patients and continued tumor cell survival and proliferation. The Office Action states that Taplin does not disclose an in vitro drug screening method which is allegedly supplied by Joly-Pharaboz recitifies in its disclosure. The Office Action states that Joly-Pharaboz disclose drug selection for androgen-responsive cell lines in vitro under culture conditions with chronic treatment of androgens and antiandrogens, where cell proliferation under long-term culture is used to assess induction of drug resistance, but that the claimed time periods are not taught. These deficiencies are said to be overcome by the alleged teachings of Culig and Haapala as set for the above.

Applicant submits that there can be no reason, other than the disclosure of the instant application, to combine the references in the manner suggested in the Office Action. The MPEP Section 2143.01(IV) states:

A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art **is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references.** *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). **"[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."** *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396 quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). [emphasis added]

Applicant submits that the mere fact that all of the instantly claimed elements can be identified in the cited art does not make the instantly claimed invention obvious in view of the cited art.

Further, the combination of Long or Foury with Culig and Haapala fails to teach or suggest that an antiandrogen-resistant cancer cell line that expresses a mutant androgen receptor having the same mutations as those clinically found in patients administered with the antiandrogen can be produced by culturing cancer cells sensitive to an antiandrogen for a long time (6 weeks or 13 weeks) in vitro.

Therefore, even when the method disclosed by Long, Foury, Taplin and Joly Pharaboz is modified after being motivated by Culig and Haapala, it cannot be predicted that

a long-term culture of cancer cells in the presence of an antiandrogen can induce the same resistant cancer as that clinically found. Moreover, none of the references teach or suggest that an effective antiandrogen drug that does not induce a resistant cancer can be selected in long term culture as claimed.

Rejections under 35 U.S.C. §102(b)

The Office Action has rejected claims 12, 71, 72 and 77 under 35 U.S.C. 102(b) as allegedly being anticipated by Foury et al (J. Steroid Biochem. Molec. Biol. 66:235-240 (1998); cited in the PTO 892 form of 5/15/07) in view of Culig et al. (Br. J. Can. 81:242-251 (1999); cited in the PTO 892 form of 1/12/07) and Haapala et al., (Lab. Invest., 81: 1647-1651, 2001); cited in the IDS of 12/2/04).

Applicant respectfully disagrees for at least the reason set forth by the Examiner in the Office Action. Applicant notes that "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The Office Action states, "Foury **does not teach** culturing for at least 6 weeks or at least 13 weeks" (top of page 15).

Therefore, by the statement of the Office Action, Foury cannot anticipate the instantly claimed invention as Foury **does not teach** each and every element as set forth in the claims. Withdrawal of the rejection is respectfully requested.

In view of the above amendment, applicant believes the pending application is in condition for allowance. Upon indication of allowable matter, Applicant request that the Examiner consider if rejoinder of any of the withdrawn claims would be possible. If rejoinder is not possible, Applicant will cancel the withdrawn claims to allow the remaining claims to proceed to allowance.

Request for Extension of Time and Fee Authorization

The Commissioner is hereby authorized to charge Deposit Account No. 04-1105 referencing Docket No. 68138(46590) the fee for a one month extension in time for reply, large entity. Applicant believes that no further fee is due at this time. Nevertheless, the Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105 referencing Docket No. 68138(46590).

Dated: July 1, 2009

Respectfully submitted,

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